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Original Article

The Effect of the Mixture of Natural and Cellulose-Based Polymers on the Physicochemical Properties of Sumatriptan Succinate Mucoadhesive Buccal Patches

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ABSTRACT

Purpose: This study aimed to prepare and evaluate mucoadhesive buccal patches of Sumatriptan Succinate (SUS) made from natural polymers to improve bioavailability, patient compliance, and dose-dependent adverse effects associated with currently available dosage forms. **Materials and Methods:** The solvent casting method was used with a 3^2 factorial design. The base polymer was water-soluble polysaccharide pullulan at 2% m/v. NaCMC, SA, PVA, and PVP-K30 was also added in various amounts. The polymer-plasticizer solution, SUS, and SS were combined and dried before being cut into 2 cm patches. The patch was water-resistant-backed and stored at room temperature in an airtight glass jar. **Results:** The patches had a mass uniformity of 61.75 mg to 84.18 mg and a film thickness of 0.2 mm to 0.5 mm. Some formulations demonstrated excellent folding endurance, with some exceeding 300 folds. The drug content ranged from 6.0 to 9.2 mg, with high drug loading efficiency in formulation SB29 (95%). The patches surface pH ranged from 6.0 to 7.2. At 120 min, formulation SA19 showed significant swelling (70±3%) but achieved maximum drug release (100.2%) in a shorter time. Permeation studies discovered a link between drug release and permeation. Various analyses and accelerated stability tests revealed no significant changes in physicochemical properties. **Conclusion:** This study demonstrated that the prepared mucoadhesive buccal patches of SUS might be useful in treating migraines, promising improved therapeutic outcomes, increased patient compliance, reduced side effects, and cost benefits.

Keywords: Buccal patches, Unidirectional Buccal Drug Delivery, Mucoadhesion, Migraine, Sumatriptan succinate, Pullulan.

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INTRODUCTION

Pharmaceutical research is shifting from developing new chemical entities to developing Novel Drug Delivery Systems of existing drug molecules to maximize therapeutic action, patent protection, patient compliance, and reduce adverse effects and costs. Recently, interest has grown in developing drug delivery systems using mucoadhesive polymers to attach to body tissue to target absorptive mucosa like ocular, nasal, pulmonary, buccal, and vaginal. Out of this, drug administration through the buccal region is appealing due to ease of administration, patient compliance, and the need for relatively less complicated techniques. Buccal drug delivery involves drug delivery through the buccal mucosal lining.[1]

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Sumatriptan Succinate (SUS) (3-[2-(dimethyl amino) ethyl]-N-methyl-1H-indole-5-methane sulphonamide succinate), used to treat migraine, is a 5 HT-1 receptor agonist. Typically, migraine lasts up to 24 hr. Still, their duration can range from 4 to 72 hr, and patients experience migraine attacks once or twice per month.[2] SUS is traditionally administered as oral tablets in doses of 25 mg, 50 mg, or 100 mg as a single dose. However, due to hepatic first-pass metabolism, its oral administration results in only 15% bioavailability. It is also reported that the side effects of SUS can be dose-dependent. To overcome this limitation, SUS is developed as 10 mg or 20 mg nasal sprays and subcutaneous injections (6 mg, taken twice within 24 hr). These alternative formulations are unfortunately expensive, poorly received by patients, and have poor retention time.[2]

The buccal drug delivery system holds promise for addressing unmet needs in migraine treatment. By providing direct access to the systemic circulation through the internal jugular vein, this method circumvents the first-pass metabolism, increasing the

bioavailability of SUS. In addition, the buccal system features noninvasive administration, rapid onset of action, a convenient and easily accessible site for drug application, self-administration capability, low enzymatic activity, suitability for drugs or additives causing mild and reversible mucosal damage or irritation, painless administration, simple drug withdrawal, low cost, and high patient compliance.[3,4]

Therefore, this study aimed to investigate the viability of buccal-controlled drug delivery for SUS using natural polymers. The study evaluated and optimized different formulation variables that control the physicochemical characteristics and drug release from the mucoadhesive patch to achieve consistent and controlled release of SUS to ultimately improve the therapeutic outcomes for the treatment of migraine.

MATERIALS AND METHODS

Materials

For the study, the following materials were procured from specific suppliers: Yarrow Chem Mumbai, India, supplied the SUS, pullulan, and Sodium Carboxy Methyl Cellulose (NaCMC). SD Fine Chemicals, Bangalore, India, supplied all other chemicals, including Sodium Alginate (SA), Poly Vinyl Alcohol (PVA), Poly Vinyl Pyrollidine (PVP-K30), Poly Ethylene Glycol (PEG), Propylene Glycol (PG), and Sodium Saccharin (SS). Throughout the study, analytical-grade chemicals and reagents were used.

Methods

Formulation of Mucoadhesive Buccal Patches

The solvent casting technique was used to develop SUS mucoadhesive buccal patches. The formulation ingredients were optimized using a 3^2 factorial design.[5] Pullulan, a water-soluble polysaccharide, was employed as the base polymer at a concentration of 2% m/v. The patches also contained various proportions of NaCMC, SA, PVA, and PVP-K30. The formulation combinations are detailed in Table 1.

For the preparation of the patches, a clear and homogenous solution was prepared by adding 2 mL of either PEG or PG as a plasticizer to the polymeric solutions. A homogenizer (Biochem D-160, Molbiogen, Guwahati, India) was used to stir the mixture for 1 hr. Afterward, 10 mg of SUS and SS were added to the polymer-plasticizer solution and thoroughly mixed until a solution devoid of bubbles was obtained. The resultant solution was poured into Teflon-coated circular dishes 9.6 cm in diameter. The mixture was allowed to dry at room temperature for 2 hr before being dried at 60°C for 36 hr in a hot air oven (Labtronics Hot Air Oven, India). After drying, the patches were vacuum dried for 4 hr at room temperature. The dried patches were carefully detached from the Teflon-coated circular dishes and inspected for flaws or air bubbles. The flawless patches were then cut into 2 cm-diameter pieces with a stainless steel blade cutter. Pidilite® BOPP, a water-resistant backing, was applied to one side of the patch. The patch was wrapped in aluminium foil paper for storage and later analysis and put in an airtight glass jar at room temperature.[6,7]

Evaluations

Weight Variation, Thickness, Surface pH, and Folding endurance

Five different patches were selected at random for these evaluations. Patches were weighed in an electronic balance (Shimadzu TXB6201L, Japan) for weight variation (mass uniformity), and the thickness was measured using a standard screw gauge (Optec Standard Micrometer Screw guage-CHAAA010, India). The mean and standard deviation were then computed. The surface pH was calculated by leaving the patch on the surface of a 2% w/v agar plate (9.6 cm diameter) and allowing it to swell for 15 min. A pH electrode was placed on the patch's swollen surface and left for one minute to equilibrate. Three times, the experiment was run, and the average was taken. The folding endurance was determined by repeatedly folding the patch at least 300 times or until the patch broke.[8]

Drug Content Uniformity

With intermittent shaking, 10 mL of pH 6.7 simulated saliva was used to dissolve the patch without a backing membrane. The above solution was filtered through 0.46 (µm) microfilter paper to obtain a clear solution. A UV spectrophotometer (Shimadzu 1800, Japan) at a 282 nm wavelength was used to measure the concentration of SUS in the solution after dilution.[9]

Swelling Studies

The patch's diameter was measured without the backing membrane. This patch was applied to the agar plate and kept in an incubator (GLAB India Digital, India) at 37°C. The diameter of the swollen region was measured over time. The following equation was used to calculate the Swelling Index (SI) where Do is the diameter of the original patch at time zero, Dt is the diameter of the swollen patch after time 't', and SI (%) is the % swelling:

$$SI\ (\%)=(D_t-D_o)/D_o) \times 100$$

Where D_o is the diameter of the original patch at time zero, D_t is the diameter of the swollen patch after time t, and SI (%) is the % swelling.[10]

In vitro Residence Time (*Ex vivo* mucoadhesion time)

To determine the *in vitro* residence time, a modified USP 23 (Wrweka ZT72, Erweka, India) disintegration testing device was used. The equipment consisted of a beaker with a capacity of 1000 mL. To this, 800 mL of simulated saliva solution (pH 6.7) was added, and the temperature was maintained at 37±1°C. A small (2 x 2 cm) piece of the patch was cut and attached to the porcine

mucosa (3 cm). This mucosa was attached vertically to a glass slide and placed in phosphate buffer in the beaker using cyanoacrylate adhesive. The glass slide with mucosa began to move up and down as soon as the motor was turned on. It was noticed how long it took for the patch to separate from the porcine mucosa. Six different patches were tested simultaneously.[11]

In vitro Drug Release Study

The USP 23 Type II dissolution equipment was used to test the *in vitro* drug release (rotating paddle type, eight-station dissolution test apparatus, EDT-08Lx, Electrolab, India). Water was added to the water bath, and the temperature was maintained at 37°C.

Table 1: Formulation Combinations of Various Pullulan-based SUS Buccal Patches.

Formulations*		Pullulan (2% m/v) mL	PVA (2% m/v) mL	SA (1% m/v) mL	PVP K-30 (2% m/v) mL	Na CMC	SUS (mg)
SA1	SB1	15.00	10.00	05.00			10.00
SA2	SB2	13.80	09.20	06.90			10.00
SA3	SB3	12.60	08.40	08.40			10.00
SA4	SB4	12.60	08.40	08.40			10.00
SA5	SB5	12.00	12.00	06.00			10.00
SA6	SB6	11.25	11.25	07.50			10.00
SA7	SB7	11.25	11.25	07.50			10.00
SA8	SB8	10.56	14.08	05.28			10.00
SA9	SB9	09.90	13.20	06.60			10.00
SA10	SB10	11.25	07.50		11.25		10.00
SA11	SB11	13.83	09.22		06.91		10.00
SA12	SB12	11.25	07.50		11.25		10.00
SA13	SB13	12.00	06.00		13.00		10.00
SA14	SB14	15.00	07.50		07.50		10.00
SA15	SB15	12.00	06.00		12.00		10.00
SA16	SB16	09.90	12.00		09.00		10.00
SA17	SB17	10.56	14.08		05.28		10.00
SA18	SB18	09.00	12.00		09.00		10.00
SA19	SB19	09.90		06.60	13.20		10.00
SA20	SA20	12.84		08.56	08.56		10.00
SA21	SB21	11.25		11.25	11.25		10.00
SA22	SB22	09.00		12.00	12.00		10.00
SA23	SB23	11.25		07.50	07.50		10.00
SA24	SB24	09.90		09.90	09.90		10.00
SA25	SB25	10.56		14.08	14.08		10.00
SA26	SB26	13.83		09.22	09.22		10.00
SA27	SB27	12.00		12.00	12.00		10.00
SA28	SB28	15.00			10.00	05.00	10.00
SA29	SB29	12.84			08.56	08.56	10.00
SA30	SB30	11.25			07.50	11.25	10.00
SA31	SB31	15.00			10.00	05.00	10.00
SA32	SB32	12.84			08.56	08.56	10.00

*SA1-SA32: 2 mL PEG is the plasticizer; SB1-SB32: 2 mL PG is the plasticizer.10 mg of SUS was added to all formulations. The total volume of polymeric solution was 30 mL without plasticizer, drug, and SS.PVA: Poly Vinyl Alcohol; SA: Sodium Alginate; PVP K-30: Poly Vinyl Pyrrolidine K-30; Na CMC: Sodium Carboxy Methyl Cellulose; SUS: Sumatriptan Succinate; PG: Propylene Glycol; PEG: Poly Ethylene Glycol.

A 1000 mL cylindrical vessel with 900 mL of pH 6.7 dissolution media was submerged in the water bath. A glass slide was attached to the prepared patch (2 cm in diameter) using cyanoacrylate adhesive before being put into the cylinder. Assisted by a movable shaft, the paddle was rotated at 50 rpm. Samples were removed (5 mL) from the cylinder at appropriate intervals (5, 10, 15, 30, 45, 60, 90, 120, 150, and 180 min), and the same quantity of fresh buffer solution was then added (dissolution medium). A UV spectrophotometer (Shimadzu 1800, Japan) set to 282 nm was used to measure the quantity of SUS released from the patch after the samples were filtered through micro filter paper (0.46 µm).The drug release mechanism was determined by finding the best fit of the release data to Higuchi and Korsmeyer-Peppas models.[12,13]

Mechanism of Drug Release

Several mathematical models may be pertinent when studying drug release kinetics from buccal patches. The best fit to the Higuchi model was determined to establish the kinetics of SUS release from buccal patch formulations. This model can be used to explain drug dissolution from various pharmaceutical dosage forms with modified release as a square-root time-dependent diffusion process based on Fick's law.

$$Q = {}_{t}KH\sqrt{t}$$

The release mechanism deviates from Fick's equation and exhibits non-Fickian behavior in various experimental situations. A more general equation can be used in these situations. A fundamental, semi-empirical model that exponentially links drug release to pass the time was developed by Korsmeyer *et al*. in 1983.

$$Qt/Q\alpha = Kt^{n}$$

Where 'n', the release exponent, is a parameter dependent on the release mechanism and is used to characterize it. Qt/Q is the fraction of the drug released at time t. K is a constant made up of the structural and geometric features of the formulation. Peppas used this n number to describe different release methods.[13]

In vitro Permeation Studies

During the permeation study, the amount of SUS permeated through the porcine buccal mucosa was measured using the Franz diffusion cell. The porcine buccal mucosa was obtained from a local slaughterhouse and was utilized within 2 hr of slaughter. The mucosal epithelium was carefully removed from the surrounding tissue and placed between the donor and receptor compartments of the Franz diffusion cell. The patch was secured to the donor compartment's mucosal surface and continually stirred on a magnetic stirrer (BioGene BO7X95Y44C, India). PBS was used in the receptor compartment, while simulated saliva was used in the donor compartment. 2 mL of samples were taken out for evaluation at intervals of 5, 10, 15, 30, 45, 60, 90, and 120 min and was replaced with fresh medium.[14,15]

Accelerated Stability Studies and Stability in Human Saliva

Stability testing was performed for selected patches by wrapping them in aluminum foil, placing them in glass Petri dishes, and storing them for 6 months in a stability chamber at an accelerated temperature (40±5°C and 75±5% RH). The drug content, mucoadhesion time, and changes in the appearance of all formulations were evaluated at 1, 2, 3, 4, and 6 months. The data was given as an average of 3 different measurements. Additionally, the selected patches were examined in the saliva of healthy adults. The drug content and appearance were assessed by placing the patches in 5 mL of saliva at 37±0.2°C.[16]

FTIR Spectral Studies

The FTIR spectra of the optimized formulation (SA19) were recorded using an FTIR spectrometer (Alpha E Bruker ATR Module). The absorbance of the substance was measured using the potassium bromide disk method.[17-20]

Differential Scanning Calorimetry (DSC)

A DSC thermal examination of the optimized formulation (SA19) was performed to check crystallization using a DSC Q100, TA Instruments Inc, USA). The sample was placed in sealed non-hermetic aluminum pans and scanned at a heating rate of 10°C/min in the temperature range of 25-200°C.[17-20]

X-ray Diffraction Studies

The X-ray diffraction (XRD) pattern of optimized formulation (SA19) was studied using a copper target at a voltage of 40 kV and a current of 30 mA. The scanning was performed over °2 θ range of 10-80°.[19,20]

RESULTS AND DISCUSSION

Evaluation of Mucoadhesive Buccal patches

Sixty-four formulations of SUS mucoadhesive buccal patches were prepared using the solvent casting method with varied polymeric combinations of cellulose and other natural polymers as per factorial designs. Physicochemical parameters such as mass uniformity, film thickness, folding durability, drug content, drug loading efficiency, and surface pH were measured for SUS buccal patches. Table 2 shows data on physiochemical properties.

Mass uniformity is a crucial quality since it guarantees both the accuracy of the dose and the compliance of all the constituents with the limit, further ensuring consistent adhesive properties and ultimately improving drug delivery and patient experience,[21] Depending on the formulation's ingredients, the mass of the patches in the current study varied from 40 to 85 mg. The largest intra-batch variation was notably low, indicating that all

Table 2: The Physico-chemical Characteristics of Pullulan Based SUS Buccal Patches.

Formulation code	Mass uniformity (mg±SD)	Film thickness (mm±SD)	Folding endurance (times)	Drug content (mg±SD)	Drug loading efficiency (%)	Surface pH
SA1	72.43±6.0	0.4±0.003	>300	9.1±0.7	91	6.2
SA2	71.23±3.2	0.4±0.005	182	9.1±0.5	91	6.4
SA3	75.52±5.1	0.3±0.004	175	6.8±0.7	68	6.3
SA4	71.54±5.6	0.2±0.003	176	8.3±0.8	83	7.1
SA5	74.29±7.2	0.4±0.005	194	7.5±0.9	75	6.9
SA6	75.63±6.7	0.3±0.004	190	6.9±0.7	69	6.6
SA7	84.18±3.4	0.4±0.002	>300	8.0±0.3	80	6.7
SA8	80.63±2.0	0.2±0.003	185	7.2±0.4	72	7.1
SA9	81.53±2.9	0.4±0.004	169	6.0±0.6	60	7.0
SA10	82.31±3.1	0.3±0.003	175	8.0±0.5	80	6.4
SA11	81.44±4.2	0.3±0.001	185	9.1±0.4	91	6.3
SA12	83.20±5.2	0.4±0.005	196	6.9±0.9	69	6.2
SA13	63.23±1.4	0.4±0.004	>300	9.2±0.2	92	7.0
SA14	64.58±6.6	0.4±0.005	199	8.4±0.5	84	6.1
SA15	66.45±5.2	0.2±0.004	215	7.9±0.6	79	6.5
SA16	62.36±7.1	0.2±0.003	188	8.0±0.2	80	6.2
SA17	61.75±6.3	0.4±0.002	>300	8.0±0.5	80	6.4
SA18	64.23±8.1	0.4±0.002	182	6.7±0.6	67	6.3
SA19	75.53±5.1	0.4±0.006	>300	9.1±0.4	91	6.7
SA20	74.23±2.3	0.3±0.004	180	7.3±0.6	73	6.2
SA21	71.56±3.4	0.2±0.006	176	6.8±0.7	68	6.3
SA22	73.54±6.1	0.4±0.004	169	8.0±0.4	80	6.7
SA23	74.36±5.2	0.3±0.002	175	7.7±0.6	77	6.8
SA24	73.45±7.0	0.3±0.001	183	8.7±0.5	87	6.7
SA25	67.85±6.9	0.4±0.006	290	7.9±0.6	79	6.3
SA26	66.24±3.5	0.2±0.006	256	7.9±0.6	79	7.0
SA27	66.46±4.6	0.4±0.006	188	8.7±0.5	87	6.4
SA28	68.34±7.0	0.2±0.006	169	6.0±0.6	60	6.1
SA29	66.54±5.9	0.3±0.001	220	7.9±0.6	79	7.1
SA30	68.63±3.4	0.3±0.002	230	7.9±0.6	79	6.9
SA31	66.44±2.9	0.4±0.006	199	6.0±0.6	60	6.0
SA32	65.63±4.8	0.2±0.006	185	8.7±0.5	87	7.0
SB1	43.23±3.0	0.3±0.004	188	6.9±0.7	69	6.1
SB2	42.15±1.2	0.4±0.002	>300	8.1±0.5	81	6.0
SB3	41.36±4.6	0.5±0.001	199	6.7±0.6	67	6.4
SB4	43.24±5.0	0.2±0.005	210	7.5±0.5	75	6.3
SB5	42.54±6.9	0.4±0.001	175	6.9±0.4	69	6.5
SB6	44.43±3.1	0.3±0.003	179	8.9±0.7	89	6.2
SB7	47.56±3.3	0.2±0.002	185	7.3±0.6	73	6.0
SB8	46.36±5.7	0.5±0.001	196	6.5±0.6	65	7.0

Formulation code	Mass uniformity (mg±SD)	Film thickness (mm±SD)	Folding endurance (times)	Drug content (mg±SD)	Drug loading efficiency (%)	Surface pH
SB9	48.54±6.1	0.4±0.002	>300	9.2±0.1	92	7.2
SB10	47.48±4.9	0.4±0.001	210	9.2±0.2	92	7.1
SB11	46.56±5.5	0.2±0.004	167	7.4±0.6	74	6.4
SB12	45.21±5.1	0.3±0.004	183	6.8±0.7	68	6.6
SB13	51.63±6.0	0.3±0.002	169	8.8±0.2	88	6.5
SB14	50.56±2.2	0.4±0.006	230	9.0±0.5	90	6.3
SB15	52.44±4.7	0.3±0.005	200	7.7±0.3	77	6.4
SB16	51.55±7.2	0.4±0.004	>300	9.0±0.5	90	6.2
SB17	53.33±6.9	0.2±0.003	188	8.5±0.1	85	6.7
SB18	52.51±2.6	0.3±0.004	180	7.4±0.3	74	6.9
SB19	55.25±3.4	0.4±0.002	240	9.0±0.2	90	6.2
SB20	54.42±4.6	0.3±0.004	199	8.8±0.3	88	6.0
SB21	55.22±4.3	0.4±0.006	>300	9.2±0.2	92	6.4
SB22	53.50±6.0	0.4±0.001	200	7.5±0.5	75	6.2
SB23	56.25±5.7	0.2±0.005	187	6.7±0.2	67	6.3
SB24	53.20±7.0	0.3±0.005	179	8.1±0.1	81	6.0
SB25	52.56±4.6	0.4±0.006	166	8.8±0.2	88	6.0
SB26	50.45±6.6	0.3±0.005	195	7.3±0.6	73	6.4
SB27	55.21±4.8	0.4±0.006	187	6.7±0.2	67	6.5
SB28	55.36±6.0	0.4±0.006	225	7.7±0.3	77	6.1
SB29	54.03±5.9	0.3±0.005	210	7.7±0.3	77	6.2
SB30	55.45±1.8	0.4±0.006	195	7.3±0.6	73	6.0
SB31	54.65±2.7	0.4±0.006	170	7.4±0.3	74	6.9
SB32	52.36±5.4	0.3±0.005	185	6.7±0.2	67	7.0

*Mean±SD, *n*=3.

formulations showed good mass uniformity. The satisfactory mass uniformity also indicates the robustness of the process, appropriate mixing, weighing, and drying.

The thickness of an adhesive patch is an important metric since it influences patient comfort and compliance, medication release kinetics, adhesion, and retention. In the current study, patch thickness varied from 0.2±0.002 mm to 0.4±0.006 mm. The largest intra-batch variation was notably low (±0.006). Some of the designed patches demonstrated good folding endurance of >300, ensuring durability, the convenience of handling, medication integrity protection, and product quality. A patch with a high folding endurance improves functionality, dependability, and convenience for healthcare providers and patients.

Drug loading efficiency is critical for mucoadhesive patches to maximize drug delivery, minimize patch size, increase stability, reduce costs, and assure constant drug release. The patches demonstrated good drug loading efficiency ranging from 78 to 93%.

Surface pH in mucoadhesive patches is critical for mucosal compatibility, mucoadhesion optimization, medication stability, patient comfort, and regulatory compliance. The surface pH of all patches was tested, ranging from 6.0 to 7.5, indicating that the patches are not irritating to the mucosa.

Eight patches (SA1, SA7, SA13, SA19, SB2, SB9, SB16, and SB21) out of 64 demonstrated good physicochemical properties and folding endurance. As a result, these 8 patches were regarded as optimum formulations and were subjected to additional studies, including swelling studies, *in vitro* residence time, *in vitro* drug release, and accelerated stability experiments.

Swelling Studies

The swelling characteristic of mucoadhesive patches is crucial for mucoadhesion, sustained drug release, patient comfort, stability, and formulation optimization. The swelling characteristics of optimized SUS buccal patches are represented in Figure 1.

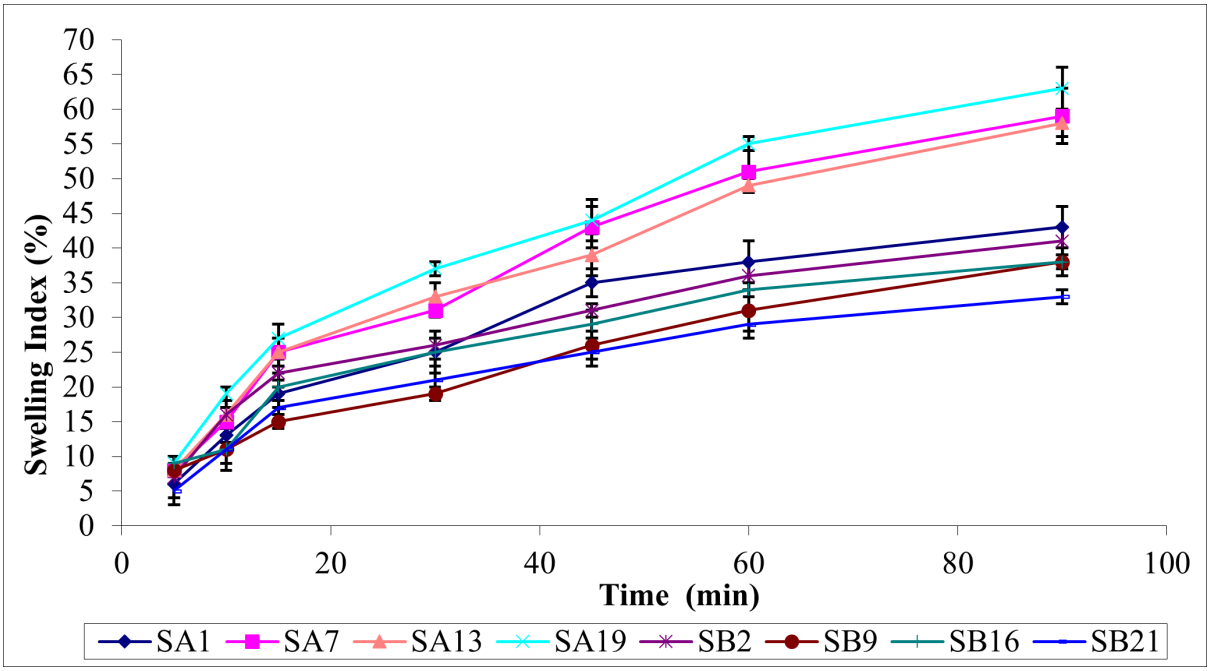

Figure 1: Swelling Characteristics of Pullulan Based SUS Buccal Patches.

Polymer concentration, cross-linking, plasticizers, pH, ionic strength, and temperature affect mucoadhesive patch swelling. Hydrophilic polymers swell more than hydrophobic polymers. Higher polymer concentrations increase swelling. Crosslinking reduces swelling, while plasticizers increase it by increasing flexibility. Ionization and solubility affect polymer swelling. Temperature-sensitive polymers can collapse to release drugs. Understanding and optimizing these factors are essential for mucoadhesive patch swelling, transitioning from swollen to collapsed states, and enabling controlled drug release.

Taking this into account, SA19 exhibits high swelling (70±3%) at 120 min due to the presence of PVP-K30, a highly water-soluble polymer, and high PEG water uptake. Patches with PEG plasticizer have a more swelling character than patches with PG. Because of the resistance of the polymer matrix to the flow of water molecules, formulation SB21 has the lowest swelling property (35±2%) when compared to SA1 (49±1%), SA7 (67±2%), SA13 (67±1%), SB2 (45±2%), SB9 (43±3%), and SB16 (41±1%).[22]

In vitro Residence Time (*Ex vivo* mucoadhesion time)

Table 3 shows the *in vitro* residence time results for optimized SUS buccal patches.

In vitro residence time affects drug release, absorption, bioavailability, patient compliance, and optimal drug distribution. Several factors affect mucoadhesive buccal patch residence time *in vitro*. These include mucoadhesive polymer type, concentration, patch size and shape, hydration and swelling properties, saliva flow and pH, environmental conditions, and drug characteristics. Selecting a mucoadhesive polymer with high mucosal affinity and optimizing its concentration increases residence time. Optimizing patch size and shape increases contact area and patient comfort. Hydration, swelling, saliva flow, pH, and environmental conditions affect adhesion, residence time, and patch-mucosa interaction.

Table 3: ***In vitro*** **Residence Time for Pullulan Based SUS Buccal Patches.**

Formulations	Mucoadhesion Time (min)
SA1	112±2
SA7	110±3
SA13	125±1
SA19	133±3
SB2	107±3
SB9	118±1
SB16	128±2
SB21	130±1

*Mean±SD, *n*=3.

The current study found that the residence time of selected patches ranged from 107 to 133 min. Tmax values for SUS administration routes are as follows: 0.17 hr for subcutaneous injection, 1.50 hr for oral and intranasal administration, and 1 hr for rectal administration. Based on the Tmax of SUS, the observed residence time was deemed adequate.

In vitro Drug Release Study

In vitro drug release testing is critical for mucoadhesive buccal patches because it ensures product quality control, aids formulation development and optimization, provides information on drug release kinetics and duration, predicts *in vivo* performance, and aids regulatory compliance. *In vitro* drug

release testing is critical for mucoadhesive buccal patches because it ensures product quality control, aids formulation development and optimization, provides information on drug release kinetics and duration, predicts *in vivo* performance, and aids regulatory compliance.

Furthermore, the ability of hydrophilic polymers to absorb water may influence the drug release rate from buccal patches, thereby increasing dissolution and, thus, the drug release rate. Figure 2 depicts the *in vitro* drug release from selected patches.

Initially, the drug, SUS, was released slowly from each patch. The rate of drug release increased significantly after 45 min. At 120 min, SA19 had the highest drug release (100.2%), sustained for up to 160 min. At 140 min, SA7 demonstrated the highest drug release (100.1%), sustained for up to 160 min. Maximum drug release percentages for SA1, SA13, SB2, SB9, SB16, and SB21 were 99.41, 99.81%, 99.18%, 98.32%, 99.1%, and 99.75%, respectively. Thus, it was demonstrated that Pullulan-based buccal patches

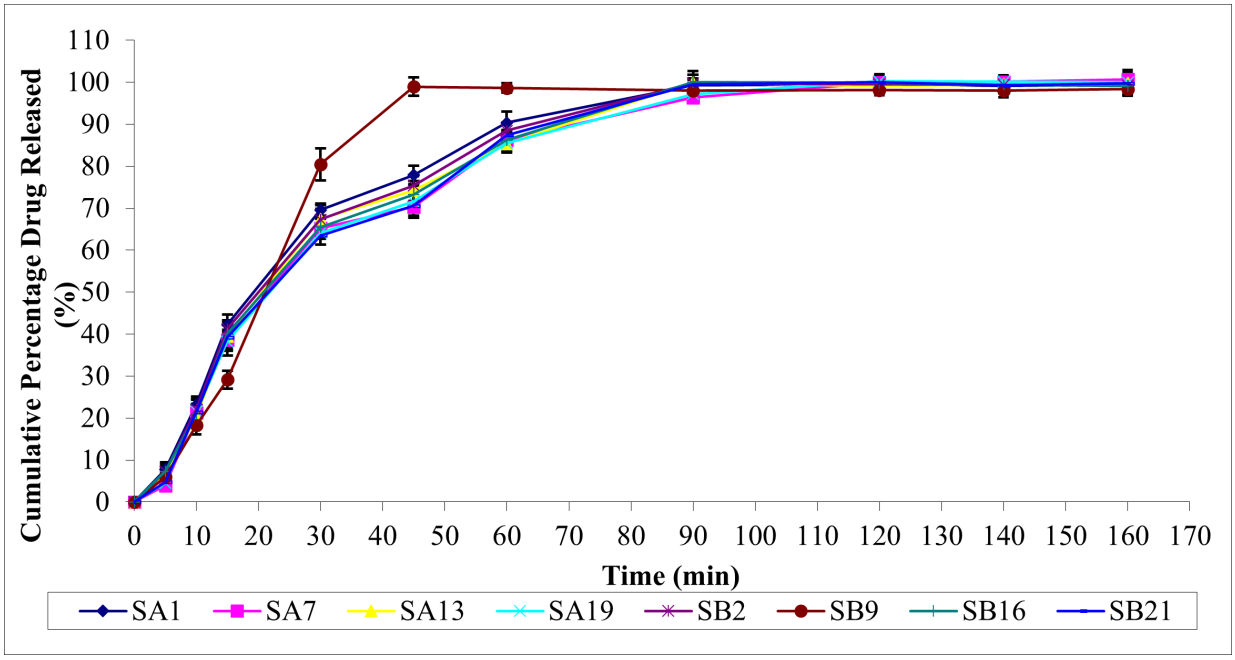

Figure 2: *In vitro* Drug Release of Pullulan Based SUS Buccal Patches.

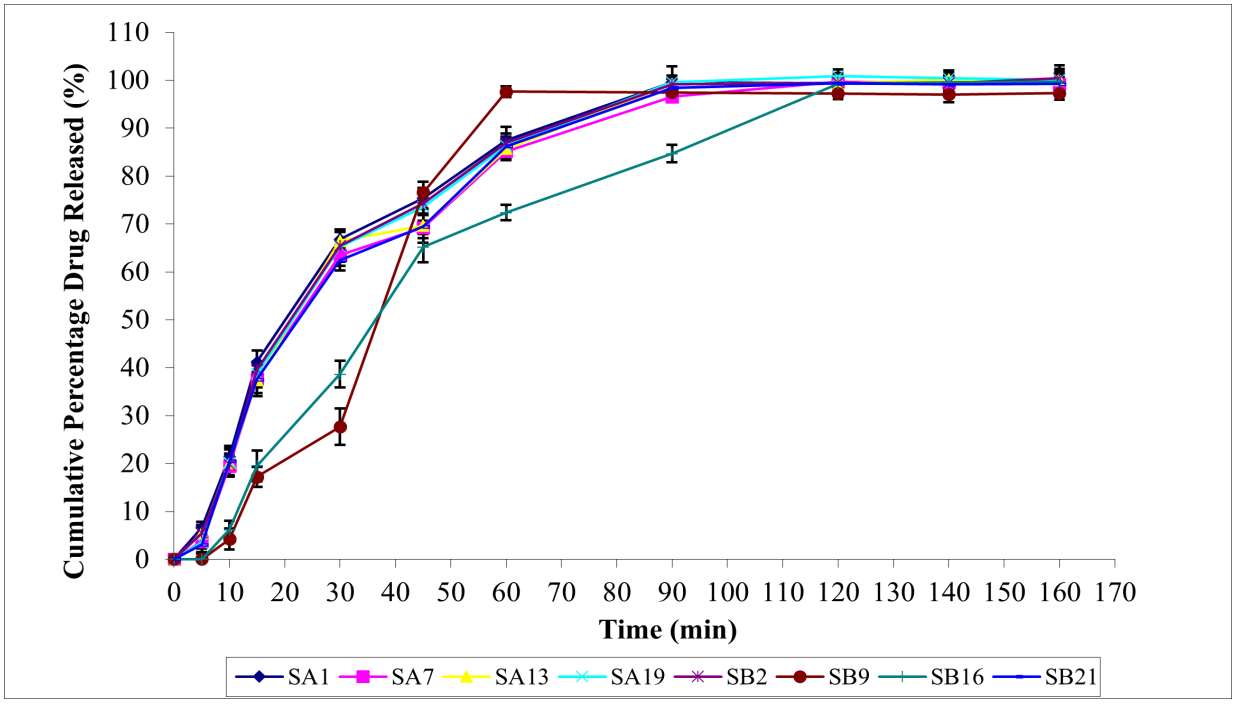

Figure 3: The Permeation Characters of SUS Buccal Patches.

containing the hydrophilic polymer PVP-K30 outperformed the other patches regarding drug release.

The Higuchi and Korsmeyer-Peppas kinetic equation described *in vitro* drug release. The release rates k and n for each model were calculated using Microsoft Excel 2003 and linear regression analysis. The precision of the fit was evaluated using correlation coefficients (r^2). Table 4 shows the values for r^2, k, and n.

Considering the r^2 values for the Higuchi and Peppas kinetic models, all the selected formulations fit the Higuchi model well. According to this model, drug release from this formulation could

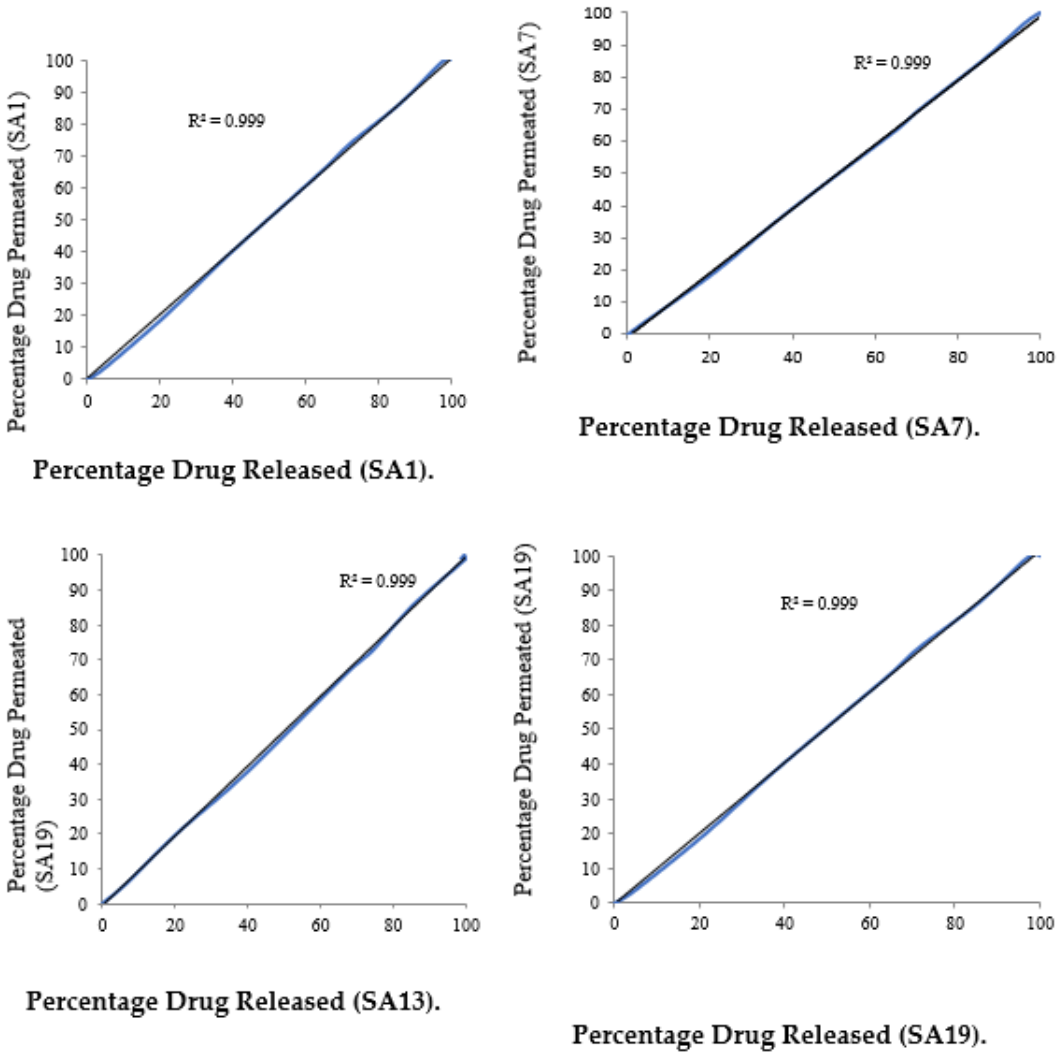

Figure 4 (a): Correlation Between *in vitro* Drug Release and *in vitro* Drug Permeation of Optimized Patches (SA1, SA7, SA13 and SA19).

Table 4: R^2, *k*,and *n* Values of Selected Pullulan Based Buccal Patches of SUS.

Formulations	Higuchi			Korsmeyer-Peppas			Mechanism of drug release
	R^2	y	k ($min^{-1/2}$)	R^2	y	n	
SA1	0.893	y=11.14x-2.502	11.14	0.699	y=0.101x-0.804	0.101	Higuchi
SA7	0.920	y=11.43x-6.606	11.43	0.669	y=0.121x-0.960	0.121	Higuchi
SA13	0.908	y=11.33x-5.160	11.33	0.704	y=0.110x-0.874	0.110	Higuchi
SA19	0.922	y=11.43x-6.537	11.43	0.685	y=0.118x-0.933	0.118	Higuchi
SB2	0.902	y=11.43x-6.519	11.22	0.707	y=0.104x-0.831	0.104	Higuchi
SB9	0.792	y=11.41x-2.683	11.41	0.661	y=0.104x-0.831	0.114	Higuchi
SB16	0.911	y=1.28 x-4.815	11.28	0.722	y=0.106x-0.844	0.106	Higuchi
SB21	0.916	y=11.41x-2.683	11.42	0.685	y=0.117x-0.925	0.117	Higuchi

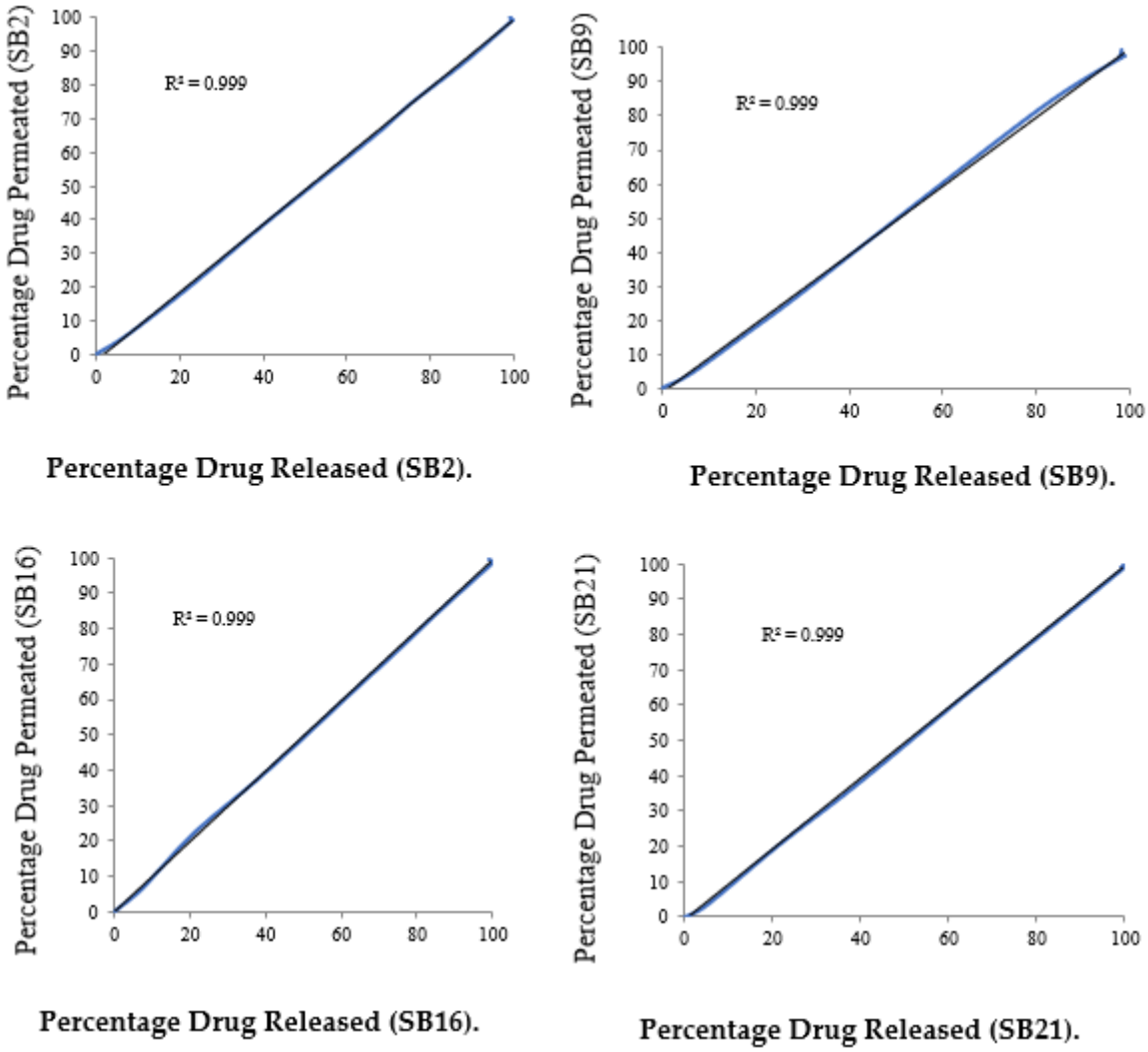

Figure 4 (b): Correlation Between *in vitro* Drug Release and *in vitro* Drug Permeation of Optimized Patches (SB2, SB9, SB16 and SB21).

be caused by micropore diffusion. The drug release rate from matrix-based devices increases when the drug loading exceeds the matrix's solubility. Fickian drug release is distinguished by the released drug's concentration-dependent linear dependence on the square root of time. The basis of diffusion is Fick's rules, which show the macroscopic movement of molecules due to a concentration gradient. When the drug: polymer ratio increases, the drug release mechanism becomes Fickian or diffusion-based. This discovery could be attributed to the dispersion of the release medium, which solubilizes the drug and causes the buccal patches to slowly release the medication.[23,24]

In vitro Drug Permeation Study

In vitro drug permeation from mucoadhesive buccal patches is influenced by several factors, similar to *in vitro* drug release. These factors include mucoadhesive polymer selection, drug properties such as molecular weight and lipophilicity, patch formulation components such as excipients and concentrations, patch thickness, pH and buffering capacity, permeation enhancers, and environmental factors such as temperature and agitation. Permeation enhancers change the properties of the mucosal barrier to increase drug permeation. *In vitro* drug permeation study data are presented in Figure 3.

With correlation coefficients of 0.893, 0.920, 0.908, 0.922, 0.902, 0.792, 0.911, and 0.916, respectively, for SA1, SA7, SA13, SA19, SB2, SB9, SB16, and SB21, SUS permeation demonstrated a pattern resembling that of *in vitro* drug release. At 120 min, SA19 showed the highest permeation rate (100.8±4.2%). While other formulations (SA1, SA7, SB2, SB9, SB16, and SB21) only reached maximum drug permeation at 160 min, ranging between 97-100%, SA13 demonstrated drug permeation of 100.1±2.3% from 140 min on. This study found a significant correlation between vitro drug release and *in vitro* drug permeation.

The correlation between *in vitro* drug release and *in vitro* permeation was studied and plotted in Figure 4 (a-b).

Table 5: Accelerated Stability Study of Pullulan-Based SUS Buccal Patches.

Evaluation parameter	Formulation code	1st month	2nd month	3rd month	5th month	6th month
Drug content (mg)*	SA1	9.0±0.7	9.0±0.8	8.9±0.8	8.9±0.9	8.8±0.9
	SA7	8.9±0.3	8.9±0.4	8.7±0.4	8.7±0.5	8.6±0.5
	SA13	9.1±0.3	9.1±0.4	9.0±0.4	8.8±0.5	8.8±0.3
	SA19	9.0±0.3	8.9±0.4	8.9±0.4	8.9±0.5	8.8±0.5
	SB2	9.1±0.4	8.9±0.5	8.8±0.5	8.8±0.6	8.7±0.6
	SB9	9.1±0.2	9.1±0.3	9.0±0.3	8.8±0.3	8.8±0.4
	SB16	8.9±0.5	8.9±0.6	8.8±0.4	8.8±0.6	8.7±0.7
	SB21	9.2±0.3	9.1±0.4	9.1±0.5	8.9±0.5	8.9±0.6
Residence time (min)*	SA1	110±2	110±3	109±3	109±4	108±4
	SA7	106±3	106±4	105±4	105±5	104±5
	SA13	124±2	124±3	123±3	122±3	122±4
	SA19	132±3	132±4	130±4	130±5	128±5
	SB2	106±3	106±3	106±4	105±4	104±4
	SB9	117±1	117±2	115±2	114±3	114±4
	SB16	124±2	123±2	122±2	122±3	121±3
	SB21	125±1	124±1	124±2	123±2	123±3
Appearance	SA1	No change	No change	No change	No change	Change in texture
	SA7	No change	No change	No change	No change	No change
	SA13	No change	No change	No change	No change	No change
	SA19	No change	No change	No change	No change	No change
	SB2	No change	No change	No change	No change	Change in texture
	SB9	No change	No change	No change	No change	Change in texture
	SB16	No change	No change	No change	No change	Change in texture
	SB21	No change	No change	No change	No change	Change in texture

*Mean±SD, *n*=3.

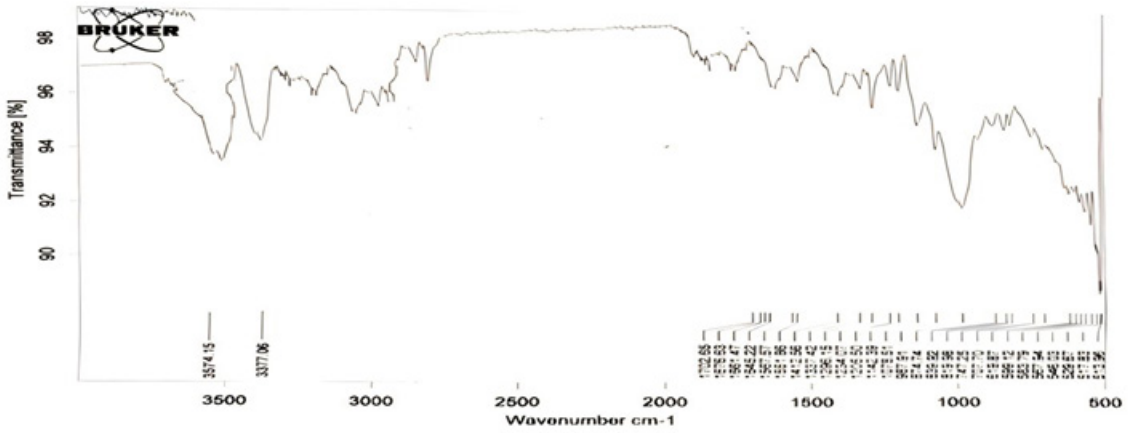

Figure 5: FTIR Spectral Studies of Selected Formulation SA19.

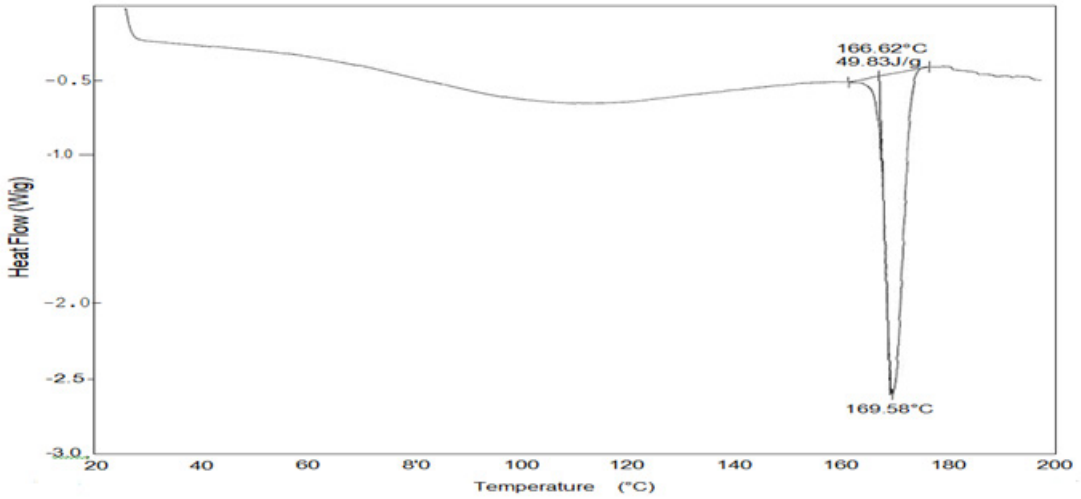

Figure 6: DSC Thermal Analysis of Selected Formulation SA19.

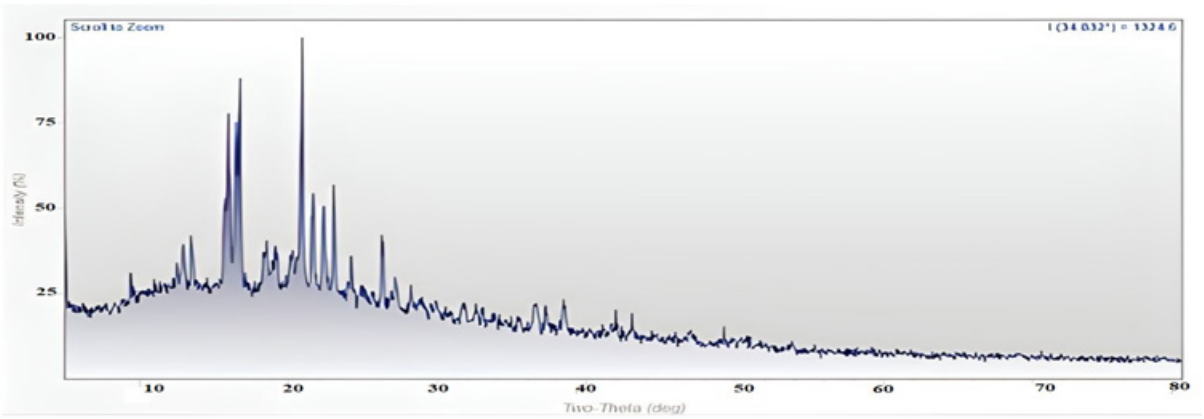

Figure 7: XRD Pattern of Selected Formulation SA19.

Accelerated Stability Studies

Table 5 shows the results of six-month stability studies on selected patches. Under accelerated conditions (40±0.5°C and 75% RH), selected patches showed no discernible changes in drug content, residence time, or appearance. Human saliva stability was also tested, and minor changes in appearance were observed. The drug content and residence time ranged from 9.0±0.7 mg to 8.9±0.3 mg and 130±3 to 105±1 respectively.

FTIR Spectral Studies

FTIR spectra of the selected formulation (SA19) are given in Figure 5.

The spectra show the main peaks around the necessary wave numbers, such as aliphatic primary amine at 3374 cm^{-1}, OH stretching vibrations at 3574 cm^{-1}, hydrocarbons (alkane,alkene, and CH bond) at 1142 cm^{-1}, 1296 cm^{-1}, 1205 cm^{-1}, and sulfonyl group at 1337 cm^{-1}. This could demonstrate no interaction between the drug and the polymers. As a result, the purity and integrity of the drug were preserved in the formulation.

Differential Scanning Calorimetry

Figure 6 shows the DSC thermal analysis of optimized formulation (SA19).

The selected mucoadhesive buccal formulation SA19 was subjected to DSC analysis. The results showed that the sample remained stable up to a temperature of 169°C. This finding implies no interactions between the drug and the polymers used in the formulation were observed. The DSC analysis revealed important information about the formulation's thermal behavior, confirming its stability within the tested temperature range.

XRD studies

The XRD pattern of the selected formulation (SA19) is shown in Figure 7.

Using an X-ray diffractometer, the XRD patterns were detected. The diffraction degree was measured at a scanning rate of 40/min. The drug and polymers individually exhibit intense crystalline peaks in the 10- to 40-degree range; however, in the optimized formulation, the peak intensity varies significantly, indicating a

change in crystalline nature due to intermolecular interactions. However, when this observation is interpreted in conjunction with DSC and FTIR spectra, it can be concluded that the formulation was stable under test conditions.

CONCLUSION

This study investigated the viability of using natural mucoadhesive polymers for buccal-controlled drug delivery in treating migraines. Through exhaustive evaluation and optimization of formulation variables, the study was able to achieve controlled and consistent drug release. The formulated patches displayed desirable physicochemical properties, including uniformity, adequate thickness, and durability. In addition, the drug loading efficiency, SI, *in vitro* residence time, and *in vitro* drug release profiles were suitable for buccal mucoadhesive delivery of SUS. The Higuchi model accurately described the kinetics of drug release, and a correlation was observed between drug release and permeation. Stability tests confirmed the integrity and drug content of the patches. This study demonstrated the potential of mucoadhesive buccal patches for controlled drug delivery in migraines, promising improved therapeutic outcomes, increased patient compliance, reduced side effects, and cost benefits.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SUS: Sumatriptan Succinate; **NaCMC:** Sodium carboxy methyl cellulose; **SA:** Sodium Alginate; **PVA:** Poly Vinyl Alcohol; **PVP K-30:** Poly Vinyl Pyrrolidine K-30; **PG:** Propylene Glycol; **PEG:** Poly Ethylene Glycol; **SS:** Sodium Saccharin; **RH:** Relative Humidity; **SI:** Swelling Index; **DSC:** Differential Scanning Calorimetry; **XRD:** X-ray Diffraction; **FTIR:** Fourier Transform Infrared.

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